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THE BOOKS OF ALL DESTINATIONS

THE TREATMENT OF HELMINTHS

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THE TREATMENT OF HELMINTHS

From the earliest times in the history of mankind an effort has been made to alleviate and cure disease. For thousands of years the only reason for applying a remedy in a given case rested upon the belief, not necessarily the fact, that it had done good in an earlier case which presented a similar chain of symptoms or signs. This plan, of course, is subject to many errors.[1]

A very large and invaluable part of our methods of treatment of helminths at present must rest upon the results of clinical observations. When a plan of treatment does good in a large series of cases identical in character, v.g. uncinariasis-ascariasis, it is a justifiable assumption that its effects are real.

With the advance of chemistry, the active principles of drugs were separated, understood and employed.

It is evident that medicinal substances used for the treatment of helminths may exert an influence on the body in many different ways.

The readiness with which a drug is dissolved or broken up in the organism greatly affects the quickness and severity of its influence.

The cells of the body may possess properties which render them immune to the effects of compounds, intact or broken up, v.g., the cells of the intestinal membrane are impermeable to a strong solution of magnesium sulphate in the bowel which acts as a purge, but if injected into the blood, it is a powerful poison.

Many cells otherwise susceptible escape because they have the power of oxidizing the substances or of destroying it before it can do harm. In some manner, which we do not understand, cells of the body possess the power of becoming accustomed to the presence of a given substance, provided its amount at first is not so great that the cell is destroyed at once, as is the case of bata-napthol for Fasciolopsiasis.

The chemical constitution or function of a cell may render it especially susceptible to a given agent as chloroform in uncinariasis which combines with the lipoid or fatty portion of the cells of the higher nervous system and glycogenetic organs.

Since the recognition of the fact that many of the disorders of function in the body and actual disease came about because of the presence of parasites, directly or by producing poisons during their life or after their death destroyed the cells of the body of men as completely as

destructive agents, it became clear that it was necessary to destroy these malign agents who invade and live by preying upon the body.

Much cannot be said as to the protective powers of the body in defending itself against helminths. Little is known of such substances as antidotes or other substances to attack the parasitic worms.

There are still to be discovered suitable drugs which have a special affinity for attacking the invading parasites without exclusively destroying the highly specialized and vitalized protoplasm of man.

If it were possible to obtain the data of all those who die annually from the use of drugs which are impure or useless from weakness, there would be an alarming array of figures.

In the treatment of helminths,the uncertainty of certain products can be eliminated by using preparations which have been standardized according to the U.S. Pharmacopeia.

One of the perplexing problems of the action of drugs is idiosyncrasy. This frequently causes disappointment to both patient and doctor.

Climatic conditions offer an interesting group

of susceptibilities, as for instance, in the tropics, generally larger doses of purgatives are required than in the temperate zones because of the inactivity of the liver. The temperament of an individual is also a highly important matter to be considered. It is a fact that phlegmatic, dark-skinned individuals usually yield to drugs less readily than blondes and nervous people.

Classification of Helminths

The principal **helminths** with which one has to deal are those which are stationary, more or less with the host and have a periodicity; spend a given period of their life in host, as the hookworm; again, the permanent parasites such as trichinae, whose entire life cycle is parasitic.

The question of chance parasites in the human being should not be overlooked.

Many examples of this type are recorded as in cases of Fasciola hepatica in man, other worms, not injurious, as Oxyuris incognito.

Spurious parasites wuch as Furnia infernalis, vermis umbilicus (creations of the imagination) as well as half-digested food, Diaconthus polycephalus and striatula need no treatment.

Frequency.

Let it be known that no species of animal and no race or class of man is free from parasitic worms.[3]

The frequency of infestation depends upon personal habits of the people; v.g. Hymenolepis nana, Ascaris lumbricoides.

Pinworms are more common in children than in adults, and whipworms in negroes than whites.

Certain parasites as trichinae and taenia are likely to be more common among people who eat improperly cooked meats. In general, animal parasitism increases from temperate to tropical climates. Consult appendix attached for reasons of frequency.

Without exception, adaptation to a parisitic existence has been accompanied by simplification and retrogression. Forms that have not to hunt for their food, but receive it in soluble, assimilable state prepared by their host; that further are largely protected from the effects of external influences by their very mode of life do not need elaborate organs of locomotion or an elaborate digestive apparatus; do not need organs of protection and defence beyond the means of neutralizing the digestive influence of the juices of their host.

Nor do they need weapons of offense beyond those

necessary to attach themselves to that host and penetrate its tissues in such a way as to gain therefrom the requisite pabulum. Thus the organs of these parasites are apt to become reduced to very simple terms; limbs and organs may become rudimentary, sense organs atrophied and as in the cestides the alimentary tract may wholly disappear; nourishment being gained purely by surface absorption.

The parasites are capable of existing for considerable periods outside of the body of the host until fortuitously taken up by another or are capable of living in different forms in a succession of different hosts; or lastly and most commonly, have enormous reproductive capacity, becoming little more than animated masses of sexual glands. Enormous quantities produced and discharged, in preparation for the probability that with rare exception, these will fall upon barren ground. It is stated that Taenia saginata can produce 150,000,000 eggs per year.

Eggs and encysted stages are very resistant in some instances, to external influences, v.g. the Persian argas may live five years without food; Cysticerus cellulosae may live four weeks or so after host is dead; trichinae may live for months after host is slaughtered; eggs with thick shells are more resistant (ellworms-whipworms) than eggs with their shells, (hookworms, pinworms, dwarf tapeworms).

For this retrogression and simplification of structure inevitably carries with it a lessened capacity on the part of the individual to adapt itself to other than a very narrow set of conditions; it has reduced its method of offense and defense to a minimum and thus we find as a general rule, that a given species can only grow actively in a particular species of host, or when there are alternatives of forms, in a particular series of host.

On general principles we should not expect such parasites to set up severe disease. When forms that require a considerable period for the development of their life cycle; forms in which, further as we have noted the survival of the species by means of passage into other hosts is precarious, it would be a suicidal policy so to injure the host as to lessen its capacity to obtain nourishment or to arrest its power of locomotion and indirectly its opportunity to distribute the eggs of the parasite. And as a matter of fact we find that these larger parasites tend rather toward symbiosis, to harmonious living together, with minimal disturbance to the host,- than toward the production of states of severe disease. Nevertheless we have no indication that the presence of parasites is an advantage to the host.[4]

In 1801 Jordens held that intestinal worms are "the

good angels of unfailing helpers of children." The indications to-day are the contrary.

In order to understand to a slight degree at least, how the injury is set up by the parasites, it might be helpful to divide the evidences of disturbances according to Tearnsides,[5] viz:

(1) Injury caused by the mere presence of the parasite. In general it is nil. There are exceptions as in Filariasis when the lymph vessel or gland may set up disturbances as in elephantiasis; also Cysticercus cellulosaein the brain may cause fatal results, or in the eye may cause blindness. The larval stage of Taenia echinococcus is most dangerous as large cysts are found in the liver and elsewhere.

(2) Injuries caused by migration.

The minute larvae of Filaia nocturna make a nightly migration from the deep-seated blood vessels of the internal organs to the peripheral vessels without causing disturbances. The Dracunculus medinensis, the largest of the round worms, may without symptoms, make its way through the tissues of the body until it comes to lie under the skin of the leg, and then only sets up disturbances when it pierces the skin to allow escape of its ova, orbecomes ruptured.

A common cause of irritation and itching is the nocturnal passage outward at the anus by Oxyurs vermicularis.

A very common dermatitis is set up by the penetration of hookworm.

(3) Injury set up by active destruction of tissue. This is questionable. Hookworms probably feed upon the mucus membrane of the small intestines and according to Looss[8] suck in blood when by chance they pierce theunderlying capillaries. Loeb and Smith oppose this view and claim that the worms pierce the capillaries and that there is a discharge from the worms which arrest the coagulation of the blood. The continued minute hemorrhages may be a factor in the production of anaemia. But others question whether it is not a secondary result of the erosion, not from loss of blood but from absorption through the damaged mucosa of toxic intestinal content, if not from a subinjection.[7]

The Diphyloborthrium latum likewise attaches itself to the intestinal wall and in so doing injures the mucous membrane.

The Tricocephalus dispar[8] can bore through the intestinal wall but there is little proof that it has caused many cases of appendicitis.[9]

(4) Injury by loss of food stuffs.

According to Shipley and Fearnside , in general this

is so slight as to be negligible. A female roundworm Ascaris Cumbricoides can produce 42 grams of eggs every yearand must extract from thehost a certain amount of nutriment for herself besides the amount that goes to build up the ova.

When present in large numbers, Franconneau and Dufresne describe a case in which a boy got rid of 5,000 worms in less than three years, and in one day evacuated 600--the loss is certainly serious. Strongyloides Stercorales exist in large numbers and it is not uncommon for 100,000 to be expelled at one time. Such a number is said to weigh 200 grams.

Dr. Barlow[10] demonstrated over 3,000 Fascolopsis buskis which filled a quart jar, taken from one patient.

(5) Morbid conditions caused by excretions.

Weinland[11] demonstrated that cestodes defend themselves against the action of the digestive juices by the elaboration and excretions of an antibody--antitrypsin. These defensive bodies favor the suffocation that the parasites excrete; also offensive substances. The cyst contents of Tinea-Schenococcus[12] have been found poisonous, setting up in lower animals, when injected, peritonitis and urticaria; similar disturbances have been noted to follow the rupture of these cysts in man.

Cattaneo[13] working with Ascaris found 2 cc. of expressed body fluid would kill a guinea pig within forty hours.

Dr. Ransom[14] of Washington is very susceptible to Oescaris, developing a marked urticarial eruption from the touch of this worm.

Diphylobothrium latus sets up a most pronounced anaemia. Schauman and Tallequist[15] have produced a like anaemia in the dog, by injecting extracts of this parasite. Buckless in 1894 first showed that eosinophilia characterizes all forms of helminthiasis. All kinds of parasitic worms from the harmless oxyuris upward induce eosinophilia[16]; and as shown by Leukenstein, there is constantly the presence of Charcot-Leyden crystals in the feces.

Principles of Anthelmintic Medication.

(1) Anthelmintics are selective in their action[17]; i.e., their dependable effectiveness is limited to certain sorts of worms, depending on differences in structure, physiology and habitat.

In brief the germicidal power and insectidal power of anthelmintics are unrelated.

(2) Certain kinds of worms require not only a suitable anthelmintic but also suitable modes of medication; whereas other worms only require the simple administration of a single therapeutic dose of a suitable drug.

Raillet[18] states that in general, large worms are more vulnerable than small ones; adult Ascarids are more easily removed than larval forms or the smaller hookworms; the latter more easily than strongyloides or the small trichostrongyles. This is due probably in part to the ability of small worms to protect themselves by a position in small food masses or under mucus.

Lane[20] says "No single course of treatment by any known drug or combination of drugs can be relied upon to expel the ancylostomes which are present."

Perhaps this is due to the fact that certain groups are attached to the intestinal mucosa and other groups are detached.[21]

Another theory is that worms which were feeding at the time of treatment were susceptible to the drug; that individual worms had greater resistance or were better protected by mucus.

(3) Fluid extracts or other preparations using alcohol as a solvent for active anthelmintic ingredients are frequently unsuitable, on account of rapid systemic effects, due to absorption largely in the stomach and duodenum, leaving a small amount of drug available for the required action.

Bozzolo[22] was the first to use thymol against hookworm in 1879 and advocated the administration of a glass of strong

wine or some alcoholic mixture after each dose of thymol in capsules to facilitate solution of drug.

(4) Anthelmintics of a supposely insoluble type are not as insoluble as they are commondly supposed to be.

Seidell[23] states "of the thymol administered from one-half to two-thirds is apparently destroyed or temporarily fixed in the body.

Hall's experience in giving large or repeated doses of oil of chenopodium found that the faeces commonly have the distinctive odor of this oil, but small doses do not give this result as a rule, and must be very largely absorbed. Salant and Livingstone state that after intravenous injections of large amounts of chenopardium, it could be detected in the respired air, but not in the urine or bile.

In speaking of solvents Hall noticed that toxic drugs are rapidly absorbed and that the brunt of the irritation and insult due to the drug is borne by a rather limited section of the digestive tract, and that a great amount of comparatively concentrated drug is taken in over the gastric and duodenal mucosa, and possibly by that of the upper jejunim mucosa.

In addition to the local effects, there is the systemic effect due to the sudden imposition of a considerable amount of anthelmintic which must be disposed of by the body economy in bulk instead of piecemeal.

It is desirable to retard that absorption in order to distribute it over as large a surface of the gastric intestinal mucosa as possible and to allow the maximum time for the body gradually to disprove of the drug by oxidation and elimination.

(5) It is questionable whether some anthelmintics need time to act on the worms before purgatives are administered. Dock and Bass[24] explained the failure of remedies to act effectively as possible due"to the rapid carrying down of thymol by peristalsis to below the location of the worms", even in the absence of purgation.

From Hall's experience it is inferred that he feared more the absorption of the drug in the stomach before reaching the site of the worms. From a study of 250 dogs, the results seem to be a little better, if anything, where the drug and purgative are administered simultaneously, than where the anthelmintic is allowed to precede the purgative by an hour or longer. Such combinations as oil of santorin and castor oil, oil of chenopodium and castor oil; santonin and calomel seem to be effective as the ingredients of the combinations administered separately and at intervals.

(6) Preliminary fasting is important. Although this proposition is generally accepted yet an occasional writer

seems to regard it as of little importance.

When a drug is administered on a stomach full of food, it is diluted to a point where it excites the minimum amount of effect on the worms, and sometimes a drug of known potency in adequate therapeutic dose will fail to bring away any worms when given to experiment animals under these conditions.

Attempts to treat animals, like sheep and swine, by the administration and anthelmintics in the food have resulted in failures, or indifferent results, and it appears that such a line of treatment would have to be prolonged and repeated, over long period to attain any reasonable success, with all that such repetition might involve in the way of cumulative toxic results.

(7) Gastric stasis might occasionally interfere with the efficacy of anthelmintics, as shown by post mortem findings on experimental dogs.[25]

(8) The passage of worms following treatment is a better indication for repeating or continuing treatment than for stopping treatment, as is practised by many medical men.

When a well selected treatment finally fails to bring away worms, it establishes a fair presumption to the effect that all worms of the sort involved have been removed.

This could be checked by examinations, at least for two weeks, of the faeces for parasitic eggs.

(9) Severe helminthiasis calls for caution in administering anthelmintics.

A feeble, emaciated patient suffering from enteritis as a result of numerous worms, and with the bodily resistance already much lowered by worm toxins, is itself a contraindication for treatment both as regards the production of local irritation in the digestive tract and the production of systemic effects.

Stiles-Leonard[26] and the writer noted the value of using repeated small doses of anthelmintics in such cases and the need for preliminary building up of the bodily resistance by nutritious food and tonics.

(10) The majority of the worms passed after anthelmintic treatment come away in the first 24 hours after treatment; but there is a fair percentage which will commonly come away from one to six days. Perhaps this delay is due to a poisoning of the worms which weakens or sickens them to a point where they are brought away some time after the anthelmintic treatment; or in other cases, may be due to intestinal stasis which may not be overcome by the purgation employed.

According to Hall's experience, the greater per cent. of the total number of worms passed which come away the first

day is in this order. Taenia, Dipylidium, Ascarids, Hookworms, Whipworms.

The Value of Anthelmintics and Their Administration.

Anthelmintics are drugs which are used to kill or remove intestinal parasites.

In order to possess any value, the drug must act more strongly on the parasite than on the host, and this more intense effect may be attained either by a specific action on the parasite or by the drug failing to be absorbed from the alimentary tract. As a matter of fact, the anthelmintics have not been shown to possess any such specific action. but seem to injure most forms of living tissue. Anthelmintics are often divided into vermicides and vermifuges, according as they kill or merely cause the expulsion of the worms; but as this is determined largely by the quantity which comes in contact with the parasite and the rapidity which which the bowel is evacuated, the distinction is imaginary.

Again let me state the importance of understanding the conditions that must be met with in the treatment of parasites. In the case of hookworms, for instance, their heads are imbedded in the mucosa and their bodies surrounded by mucus and food. A number of drugs have been recommended for the ex-

pulsion and treatment of helminths. In this paper, only a brief discussion can be outlined.

(a) Thymol.[27] Derived from the oil of thyme and other volatile oils and occurs in large crystals. Almost insoluble in water but is freely soluble in fats, oils, alcohol and vinegar; hence when given internally can not be given in combination with these ingredients.

In my series of some forty cases treated at the Marine Hospital, Wilmington, N.C. in 1914, I used the routine method of the United States Public Health Service as advocated by Stiles.[28]

1. A very light supper and a purge the night preceding the treatment
2. No foodexcept black coffee for breakfast.
3. First dose of thymol at 6 A.M. one half of the total dose of thymol. At 8 A.M., one-half the dose. at 10 A.M. Epsom salts. (Never castor oil).
4. Patient remains in bed until afternoon.

Dock and Bass recomended the following instructions to be given the patient.[29]

(1) Milk or light diet day preceding treatment

(2) Sodium sulphate (oz.i) the night before.

(3) Administration of 20 grains thymol at 6 A.M.

(4) " " 20 grains thymol at 7 A.M.

(5) " " 20 grains thymol at 8 A.M.

(6) " " 1 oz. Epsom salts at 10 A.M.

Drink nothing but a little water until 4 P.M. and remain in bed. After 4 P.M. arise and eat whatever you desire and do what you like.

In determining the dose in our cases, the apparent age rather than the real age was considered, and cutting down the dose when cardiac symptoms and other unfavorable conditions were present.

The following doses represent the maximum amounts to be used during one day's treatment for the age group in question. This group is used by Ashford,[30] King,[28] Stiles, Dock and Bass[29] as being a safe practical guide.

Ages (in size)	grains	grains
Under 5	7-1/2	0.5
5-10	15	1.0
10-15	30	2.0
15-20	45	3.0
20-60	60	4.0
Over 60	30-45	2.0-3.0

In a study of 259 treatments, Stiles[31] found that 205 cases complained of unpleasant effects. The most common complaint was of a sickness at the stomach (nausea) which was present in 66 treatments (14.2%). In some instances, this condition was clearly due to the thymol, but in the other instances, it seemed to be due to the salts.

The second most frequent complaint was of "weakness" which was noticed in 62 cases (13.3%). The explanation of this

is due partly to drugs, salts and fasting.

The third complaint in order of frequency was of a "burning in the stomach" following thymol, in 45 patients (9.7%).

Next comes dizziness "including giddiness" "staggery" (drunk) occurring in 44 treatments (9.4%). Headache occurred in 14 cases (3%) and vomiting in 13 cases (2.8%) were almost equally frequent.

The rest of the cases offered small groups of minor discomforts as sleepiness, chills, fainting, etc.

In general it may be stated that patients feel better when they remain in bed as much as possible until dinner time, but some do not, and yet suffer no ill effects.

Because of various reports regarding the effects of thymol, not a few persons have considerable fear of the drug; and reports of sickness or of death during treatment have undoubtedly been a very important factor in inhibiting others from continuing the treatment.

Eleven deaths have occurred up to 1913 during thymol treatment. Some of these followed the use of castor oil; and some, to the failure in carrying out the proper treatment.

Stiles believes that thymol and salts alone, without the addition of a sanitary privy will not eradicate hookworm disease.

Contra-indications for thymol administrations

(1) No food from the time of the first purgative until after the final dose of salts has acted.

(2) Alcohol, oils, gravy, butter, milk, or other fatty foods during the period of treatment.

(3) Fevers, especially malaria, and acute fevers.

(4) Diarrhoea, organic cardiac and renal disease, advanced tuberculosis.

(5) Extremely weak or feeble from old age. Pregnant women or women with serious hemorrhagic disease of the uterus.

The Int. Board of Health[32] administers thymol in the above conditions under very rigid control during the treatment.

B. Beta-napthol. A monatomic phenol occurring in coal tar, but usually prepared from naptha alone. It occurs as a colorless or pale buff-colored shining crystalline laminae, or as a whit-yellowish powder, having a phenol-like odor, and a sharp, pungent but not persistent taste. For several years, the drug has been used in the treatment of the hookworm disease. Experience shows that small doses, 0.5 to 1.0 grains, while slightly toxic, have low anthelmintic power. Darling[33] and others found that a single treatment with 40 grains removed only 26.77% of the worms present.

Hackett, in a series of 1,114 cases discovered that

two doses of the drug each consisting of 4.5 grains cured but 22% of cases treated.

Bazma and Alves,[33] in a series of hospital experiments in Brazil, treated a number of cases with 18 grains of this vermifuge. The cases received a preliminary purge on the evening before treatment, and on the following day, were given 6 grains of beta-napthol in six divided doses, administered on 3 successive days, until the 18 grains had been given. A saline purge was administered on the final day of treatment, two hours after the last capsule had been taken.

Gonzaga and Lima,[33] in a series of 400 severely infected cases, treated by this method during 1918 report 73.5% cured.

Smellie, in Brazil in 1919, conducted experiments with large doses and produced severe toxic symptoms, In 4 patients, the red blood cells were destroyed in great numbers, with resultant anaemia, icterus, haemoglobenuria, enlargement of the spleen, liver and gall bladder.

It may be possible that patients who had a recent attack of malaria with fragile red blood cells are more sensitive to the toxic action of the drug than others.

Barlow who recently returned from the endemic centre of Fasciolopsis buskii in China, gave a lecture to the helmintological students of Dr. Cort in which he demonstrated large

quart jars of flukes expelled by the beta-naphthol, a wonderful and amazing number of parasites. He himself has taken as high as 70 grains per day for self-treatment of this infestation.

C. Aspidium. (male fern) the dried rhizome of Dryopteris Marginalis. The active constituent of this remedy was supposed to be filicic acid by Poulson, but Boehm has found other neutral acid bodies present, such as aspidinin, planaspidic acid, abaspidin and aspidinol. These bodies are all derived of phloroglucin and butyric acid. It is still uncertain whether the effects of male fern are attributed to any one of them or whether all of them may notshare in the action.

The extract of oleotsein of male fern is the only one used in medicine. As a general rule it passes through the bowel without causing any symptoms whatever. The quantity of active substances dissolved while sufficient to destroy the parasite is too small to produce any effect on the host, and escapes with the other contents of the bowel. In some cases, however, where large quantities are administered, or where some unknown condition favors absorption or retention of an unusually large amount of the active constituents, grave and even fatal symptoms may supervene. These consist in vomiting, and purging, with acute pain in the abdomen, muscular weakness, confusion

and somnolence, with occasional twitching of the muscles or slight convulsive movements, collapse, coma, and death. In some cases, permanent or temporary blindness has resulted from neuritis and subsequent atrophy of the optic nerve.

The oleoresin should be administered in doses of 0.5 to $z\bar{i}$ in capsules.[34]

Poulsson recommends that oily substances be avoided during the "cure" as they dissolve the active bodies and thus promote their absorption. It must be used cautiously in cases with marked anaemia, general debility and chronic alcoholism, cardiac and renal diseases.

D. Santonin. A neutral principle derived from Levant wormseed or Santonica, which is the unexpanded flower-heads of Artemesia panciflora, a plant of Asia Minor and Turkestan.

Owing to its insolubility in water, santonin has only a slightly bitter taste in the mouth. It is partially dissolved in the stomach and absorbed, but enough passes into the bowel to effect the removal of some forms of intestinal worms. A certain amount of absorption occurs in every case as is shown by the disorders of color vision and by the yellow coloration of the urine. At first objects appear of a bluish color to the patient;[35] but this aberration is of comparatively short duration and may in fact pass unnoticed. It is fol-

lowed by a much longer period of "yellow sight" or xanthopsia. Such symptoms as rolling of the eyes, grinding of the teeth, flexion and extension of the neck and rotation of the head from side to side, point to changes in the central nervous system. It undergoes some oxidation in the tissues and is excreted in the fœces and urine, which is of a deep yellow color.

Schroeder[36] states that santonin solutions were by no means fatal to helmints, and explains their therapeutic effects by supposing that santonin renders the intestine so unpleasant an abode for the parasites that they migrate from it voluntarily into the large bowel and are carried out by the purgative. The worms are often found in active movement when passed after santonin, although this movement ceases very soon afterward from the exposure to cold.

Santonin is best given in the form of a troche or lozenge in one grain dose. Care must be used so as not to use the Trochesci Sodii Santoninatis of the U.S.P. of 1880.

Xanthopsia requires no treatment and is not to be regarded as heralding any dangerous developments.

E. Cusso and Granatum[37] are of no importance to-day.

The tannate of pelletierine has a specific action on tape-worms but no effect upon the other intestinal worms.[38]

F. History of Chenopodium.

Chenopodium, American wormseed, or Jerusalem oak, grows in the waste places from New England to Florida and westward to California.[39] Cultivated in Maryland, the oil has been known as Baltimore oil in contradistinction to the western oil which is no longer much of a commercial factor. Interest in the renewal of this oil seems to date back to Brüning in 1906 who, with Grebel, Kobert and others, investigated the pharmacology of the oil. In 1912, Schuffner and Verwort[40] presented to the 15th International Congress in Hygiene and Demography a paper in which they sought to demonstrate the superior advantage of oil of chenopodium in the treatment of hookworms as compared with other vermifuges.

Schimel reports that the acreage put to wormseed increased from about 90 acres in 1910 to perhaps 225 acres in 1912; while the yield rose from 2800 pounds to 6700 pounds in the latter years.

Composition of Oil of Chenopodium.

The investigation of the chemical and physical characteristics of this oil was suggested by the peculiar results obtained when it was mixed with petroleum oil and administered to dogs.

Kremers[42], in attempting to distill it at atmospheric pressure, found that decomposition of an explosive character occurred when the oil was heated to boiling temperature (100° C.).

Schimmel & Company[41] at 5 mm. pressure found that the oil began to distill at 53° C., 25% coming over at 53° to 79°. At 83 they obtained a fraction which constituted the principal part of the oil and to which they gave the name of ascaridol. Nelson[43] found different results than those obtained by Schimmel.

Hall obtained a distillation at about 50° and the oil completely distilled at 100° C except a gummy residue amounting to about 5%. The different fractions were found to be different in anthelmentic activity: the fraction having the lowest boiling point and the highest optical rotation is the most efficient.

Experimental Data.

A series of experiments on animals although not entirely satisfactory, seemed to show the following: Oil of chenopodium dissolves to a large extent in petroleum and that 5 times its volume with 0.7 per kilo of oil has an anthelmintic efficacy of zero; when joined in double the M. L. D., death ensues inside of 48 hours due, in part, to the irritant effects of the approximate 0.1 mil per kilo of insoluble material

present , and in part to the large dose of oil.

The indings of the ascaricidal values and thepost mortem findings of the digestive tract are as follows:

In the standard dose at the rate of 0.1 mil per kilo, the ascaricidal efficacy is 0, 0, 14, 26, 33, 100, 100 and 100% with no conclusions in two cases. In more than the standard dose: at the rate of 0.6 per kilo the ascaricidal efficacy was 100% in 4 cases, with no conclusion in one case.

In these experiments, .30 mils of castor oil was given at the rate of 0.1 mil per kilo of oil, with an efficacy of 100% in nearly all cases;but with the heavier constituents at the same rate of dosage, there was a falling off in efficacy. These experiments conclusively prove that the heavier constituents of oil of chenopodium have a diminished ascaricidal efficacy and probably an irritant character tending to the production of inflammation and haemorrhage of the gastro-intestinal mucosa.

Administration of Oil of Chenopodium.

The advantages offered by the use of soft gelatine capsules are: a convenient measured dose, tasteless,plus the advantage of bulk and bother and the assurance that the capsule will not open in the mouth, pharynx or oesophagus.

Darling, Barber and Hecker in 1918[33] criticised this

method on the grounds that with 3-10 minim doses in soft capsules at hour intervals only removed 66.4% of the hookworms present from patients as compared with the removal of 97.9% of worms by the same oil when administered in freshly filled hard capsules. The soft capsule, they claim, dissolves too slowly to permit its contents to affect the parasites distributed in the duodenum and the upper part of the jejunum, but Hall[45] thinks this to be intended only as a plausible surmise as he belives the capsules are digested or opened in the stomach.

When the soft capsules were given with purgatives, the time of opening in the stomach was materially shortened. As early as a half hour after administration and after all longer periods, the capsules were partly or entirely digested and chenopodium was detected near the ileocecal valve in 30 minutes in one instance.

In no case was the capsule found unopened in the intestine. All the evidences point to the opening of the capsules in the stómach. It becomes very much softened by exposure to the moisture of the digestive fluids of the stomach, not to mention the digestive action of these fluids. They break very easily on pressure and it seems very likely that the pressure applied to the pylorus would break these capsules if they started to pass unopened; this is hastened by increased

gstric peristalsis due to the purgatives and stimulation of secretions.

Given in soft capsules, oil of chenopodium may stay in the stomach as long as one hour, and 45 minutes if given without purgatives; or 2 hours and 7 minutes if given with purgatives. It is known that a certain amount of this drug is absorbed by the stomach, thereby adding the systemic toxic effects, in addition to diminishing the amount of anthelmintic available against the worm in the small intestine. To overcome this in actual practice, the drug was enclosed in an enteric coat. Such substances, fairly insoluble in gastric juices are used, viz, talc shellac, phenyl-salicylate-keratin and formalin-hardened gelatine, but each als its objections. It is extremely difficult to apply any capsule to burst amidst the worms in the small intestine and produce the desired action.

Results of Chenopodium.

In 1914, the writer treated 25 cases of intestinal parasites with oil of chenopodium with excellent results. In two cases of mixed infection, 56 escaris lumbricoides and about 400 hookworms were removed; in the other case, 66 ascaris lumbricoides and 600 hookworms removed.

In the original experiments made in the Orient under

laboratory conditions, two standard chenopodium treatments, separated by an interval of ten days, removed 99% of all the "hooks", harbored by a group of 39 adults. Similar treatment in Brazil during 1918, except that the work was done under field conditions, and 97% of the worms harbored were removed.

82 vagabonds more than 14 years of age at an institution in Pinheiro-Rio de Janeiro, were treated three times with chenopodium. The first two treatments consisted of 1-1/2 mil each, and the third of 3 mils. These treatments expelled a total of 10,895 worms. In this group there were 9 relative failures, or cases that harvored 10 or more after two 1.5 mil treatments had been taken.

Results in Brazil have shown that in heavily infected districts where the average worm count is 200 or more, or where the haemoglobin of non-malaricus individuals is below 60, two routine treatments of 1.5 mil each are not always sufficient, and a third treatment is advisable.

In another experiment 56 persons living on a typical coffee plantation in the State of San Paulo, Brazil, who had already been treated twice in the routine way by campaign dispensers, were given twelve days later a single dose of chenopodium. These cases were found to harbor, on the average, 5.8 worms per case after they had taken the first two treat-

ments; while four control cases treated for the first time, averaged 176 worms per case.

In 41 per cent. of the cases avery worm was expelled by the first two treatments. In 21 per cent. there was relative failure of the drug.

It was repeatedly noticed that chenopodium has a distinctly inhibitory effect upon the egg-bearing functions of the female hookworm. If the drug fails to kill the germs, however, this effect is only temporary; and after an interval, the female resumes the laying of eggs. The ova disappear from the fasces, and if the cases were not cured, reappeared the eighth to the thirtieth day.

Re-examinations should be made in not less than 14 days after the vermifuge has been taken.

Effect of Diet on Efficiency of Chenopodium.

Field experiments conducted during 1919 by the Department of Hygiene of the University of San Paulo,[32] showed that when patients were allowed their usual diet on the day before treatment, but no food on the morning of treatment, by far the results were obtained from the drug. When this procedure was followed by a preliminary purge given, 87% of the worms harbored were expelled by one treatment.of 1.5 mil; with preliminary catharsis omitted, 93.3% of the worms were expelled.

When patients were allowed no solid food after 11 A.M. on the day before treatment and no nourishment of any kind after 5 P.M. and when the preliminary purge was omitted only 75.5% of all worms were removed by one standard treatment. Moreover, prostration was universal among patients receiving this diet and their toxic symptoms were more severe than those manifested by any other group of patients.

In Ceylon[32] where the average laborer is greatly undernourished, it was found that coolies who ate an ordinary meal in the afternoon before treatment, were more or less apt to suffer collapse or syncope after medication than those who were limited to an afternoon meal of rice gruel.

In the Seychelles Islands, it was found that there was no diminution in the percent. of cures when a regular diet was permitted on the day preceding treatment.

Purgatives.

No purgative gives entire satisfaction. Magnesium sulphate has been reported upon more favorably than any of the others which have been tried.

Rapidity of action of this purgative has been found to vary in immense proportion to its concentration.

In Ceylon, with a strong solution, catharsis is delayed until evening of the day of treatment or even until

the next morning.

A weaker solution (1.5 to the ounce) gives much prompter action and is less apt to cause griping or collapse. The most satisfactory dose of the salt appears to be 2-1/2 ounce for adult male and 2 oz. for the female.

In field practice, many of the patients, after it has acted, become weak and, in some instances, are unfit for work next day, with the result that they lodge complaints against the treatment; but in hospital practice, where the patient can rest and be under constant opservation, it seems best to give it.

The original experiments of Darling and Barber and Hacker,[32] although too small in number of cases to warrant any conclusion, nevertheless showed that when the purge was omitted and the other factors were kept the same as in routine treatment, two standard soses of 1.5 mil cured 80% of the cases and removed 95% of the worms.

In a series of experiments conducted in Brazil during 1919,[32] it was found that when a preliminary purge was administered one trial, consisting of 1.5 mil of chenopodium given in two equal doses cured 29% of cases treated and removed 75% of total worms harbored. When the preliminary purge was omitted, only 14% of the cases treated were cured; but 83% of all worms removed.

The percentage of failures, cases with ten or more worms remaining after trial treatment, was 40.6% in the case of persons receiving a preliminary purge as compared with only 31 percent. for persons with omitted purge.

When the drug remains in the intestine only two hours, as in the case where it is administered in an undivided dose, a preliminary purge is necessary to aid in worm elimination; and at least a portion of it remains in the intestine for four hours, a sufficient time elapses for the drug to produce its effects whether or not the intestines have been prepared by preliminary purgative.

In field treatment given in Guatemala, Brazil, Ceylon, Scychelles Islands,[32] preliminary purgatives were omitted. No ill effects resulted in any of these cases and there was no decrease in the percentage of cures as compared with that in other years. Tests made in China during 1918 pointed towards the important part that purgatives play in removing the worms from the intestine. It was noticed that the percentage of living worms was increased if the salts acted quickly.

When the amount of salts was increased to 2 oz. instead of 1 oz. on the evening before treatment; and to 4-2/3 oz. instead of 2 oz. after treatment, 805% of 620 persons treated were found negative after one treatment. In this series, the

chenopodium was divided into two doses: one-half administered at the end of two hours; and the other half at the end of four hours following the salts. No ill effects noticed due to the chenopodium except perhaps a nausea and vomiting at times.

In Ceylon, during 1918, and the early part of 1919, the preliminary purge was omitted and a mixture of chenopodium 40 parts and croton oil, one part, was given in the standard dosage prescribed for chenopodium, graduated according to the apparent age. The dose was usually given in two equal parts with an interval of one hour between. Two hours after the last dose of vermicide, the patient received a purgative of magnesium sulphate.

Some of the features of this combination are smaller doses of salts, required to secure effective post-treatment purgation. After effects, as exhaustion, rheumatoid pains and tinnitus were much less in evidence and that nearly all the patients were able to work the following day, but some cases developed enteritis and diarrhoea which required prolonged treatment.

Chenopodium and Chloroform.

Chloroform has a higher coefficient of efficacy against hookworm than oil of chenopodium or thymol, according to Hall and Foster.[38]

Schultz[45], in speaking of chloroform says:

> "It has proved rapid in its action and so far, not followed by any evil after-effects. Should the chloroform castor oil mixture act as favorably in human beings as it has for me in dogs, it will prove a universal worm remedy of great importance."

Alessandrini[46] states its advantages: Combined with castor oil, it requires no special preparation of the patient; it can be administered at a single dose; it does not cause local or general disturbances either immediately or subsequently, and it is perfectly well tolerated and not nauseous. He advocates the use of 3-4 grain doses, dissolved in olive or castor oil, and states that it is thoroughly efficacious against hookworms, whipworms, pinworms and ascarides.

Hall and Foster[38] found its efficacy against hookworms, but less so against ascarids, and not especially so for whipworms. Chloroform is rapidly absorbed by the blood and injested by the hooks, in amounts sufficient to produce anaesthetic and lethal toxic effects. There is no evidence of synergistic action when chloroform and oil are given simultaneously; but it is possible to remove ascarids and hooks at the same time from the patient.

Chloroform.

The dose of chloroform is 2-3cc. when no contra-indications exist (liver, heart or kidney diseases) and not repeated

for at least three weeks.

Herman's mixture, of which chloroform is a constituent, the active uncinaricidal ingredient, with castor oil combined with oleoresin of male fern or oil of eucalyptus, is present in number of proprietary and trade preparations.

Bevan and Favill referred the toxic effects of delayed chloroform poisoning to toxins which could not be eliminated from the liver cells. They noticed the presence in the blood and urine of acetone, diacetic acid and beta ocybutyric acid.

Opie and Alford found that fats increased in susceptability to chloroform poisoning, while carbohydrates afforded a measure of protection against it, which accords with the clinical experience of English surgeons.

Offergeld thought that the death in chloroform poisoning is due tonephrolysis as a result of the action of the chloroform on the kidney cells.

Wells thought that the liver changes are due to the effect on the liver of the poisons which destroy the synthetic functions of the liver cells without destroying their autolytic ferments, with a resultant autolysis of the liver cells, indicated by the pesence of free amino acids, purins, protecses, peptones and polypeptids in the liver.

Whipple and Hurwitz have found that fibriniger may be almost eliminated from the circulating blood, subsequently reappearing after the repair of the liver.

Schoenhof has summarized 29 cases of delayed poisoning in man of which 17 recovered and 12 were fatal.

Farquhar used sodium bicarbonate and Jensen adrenalin with success in chloroform poisoning.

Simonds feeds sugar to his cases, which furnishes easily oxidizable material for the liver, in which the glycerin is depleted, inhibiting autolysis.

Comparison of Castor Oil and Other Purgatives.

In the Third Annual Report of the Rockefeller Foundation dated January 1917, in regard to hookworm work in Trinidad:

> "It was necessary to use magnesium sulphate instead of castor oil because of a strong local prejudice."

Darling and Barber in 1918 noted in those taking castor oil, a series of discomforts, such a dizziness, and deafness, heavy precipitates in the urine when tested for oil of chenopodium. In those taking salts, there was not this degree of discomfort or incoördination. On the other hand, is noted in the same report, a very serious mishap in a child of three years, on whom the second dose of mag. sulphate had no effect. She recovered after a dose of castor oil.

Heiser[47] in 1917 reported in the "Military Surgeon" the death of two children in Ceylon, where mag.suph. was used; and in comparing the results here with that in Sumatra where there were no deaths in 300,000 treated with oil of chenopodium, no preliminary purgation and castor oil used instead of salts.

Hall[50] and Salant[49] found that fixed oils have a value in preventing chenopodium poisoning. Castor oil, in Hall's experiments of 220 days, gave excellent result. It will save the lives of animals receiving lethal doses of chenopodium when administered with the drug or an hour later. Liquid petrolatum affords little protection and diminishes the efficacy of the drug. Olive oil retards the passage of chenopodium from the stomach and increases gastric absorption and does not protect against lethal doses.

Intravenous Injections of Chenopodium.

Salant and Livingstone[49] records show that when an emulsion of .02 to .08 cc. is injected into the femoral vein of a dog, the blood pressure falls. With a second injection, the effect was more pronounced. This fall is believed to be cardiac in origin. Likewise frequency of heart action was diminished and also a marked decrease of vagus irritability was observed.

Respiratory depression, such as decreased amplitude and rate, with apnoea, was common in dogs but less so in cats.

That the essential oils may be detroxified by glucuoric acid has been shown by Schmiedeberg, Mayer and Hildebrandt.

Large amounts of glycuoric acid were obtained after feeding grape sugar or cane sugar which might thus explain the effect of chenopodium in starvation. Its toxicity is distinctly increased in starvation and decreased by feeding oils and a rich carbohydrate diet.

Intra-Intestinal Tube Treatment.

Kantor[32] in 1918 used the tube method in the treatment of 250 cases with good results.

This method secures the concentration of the drug in the small intestine, and can quickly accomplish its work. It is feared that this method will not be widely used and hence can be dismissed from further consideration.

The general rule may be laid down that for verminous infections of the brain, bones, muscles, eye, lungs, liver, kidney, spleen, blood and lymphatics, there is no satisfactory specific medicinal treatment, although some of these may be treated surgically.

Filariasis.

Recent arsenical preparations appeared to have killed the adult worm.

O'Brien[51] killed the embryo of F. nocturna with atoxyl: 5-40 minims intravenously.

Pilcher and Pilcher[52] report a successful case with 0.6 gram of "606" but Werner states that 0.5 grams of salvarsan did not diminish the numbers.

In case of Loa loa, the Calabar swellings can be removed surgically and do not require special medical treatment.

Dracunculus medinensis.

The ancient method of gradually extracting the untreated worm by winding it upon a split stick should be avoided.

Manson[58] recommended to douch the site occupied by the parasite with cold water 3 or 4 times a day, and protect during the intervals with dressings wet with water.

The uterus empties itself rapidly; after complete evacuation no longer reacts to the water and ten extraction is easy.

Emily's method of injecting 1-1000 solution of bichloride of mercury is efficient and practical. The worm

dies and is absorbed, or may be extracted with the aid of a knife.

Turkhud[53] had good results with a lotion of sodium chloride (5%) and sodium citrate 0.5%. He found this mixture useful in early cases and also after inflammatory signs have manifested themselves as a result of improper treatment. Macfie[54] had good results from intravenous injections of 4 grains of emetin. He found that it was sufficient to cause a disappearance of the worm. It is suggested that the tartar emetic be given every other day in one grain doses until a total of 6 grains has been administered. In event of relapse or recurrence, a second course should be given.

Surveyor[55] treated a case of Distoma disease in India by emetive injections varying from 1/2 to 1 grain, besides salts and ergot. Thymol and menthol of 1.5 cc. preparations have been used intravenously for 11 days without any toxic effects.

Schistosomiasis

The Surgeon General of the United States Public Health Service, governing the medical inspection of immigrants, issued regulations in August, 1917, placing Clonorchiasis, Schistosomiasis and Paragonimiasis, the most important of fluke diseases of the Orient[48] on the list of

excludable diseases because they were considered to be incurable.

Paragonimiasis.

In endemic hemoptysis, the lungs are tunneled by Paragonimus westermanni and infiltrated by their ova. There is no hope of curing the condition, but according to Wellman[57] mild cases, if re-infection is avoided, may recover spontaneously. Association with domestic animals should be avoided as well as raw fresh water crabs.

Clonorchiasis

These flukes inhabit the gall and bile ducts, the functions of the liver are perverted by the pathological changes and becomes atrophic. In view of the beneficial effects reported from the use of salol, it is recommended as the only known drug.

Cholagogues have been tried without success. Removal of patients from endemic districts to prevent re-infection.

Choleocystotomy has been advocated by Forchheimer[56] and laparatomy by Katsurada to carry out local treatment.

Bilharziosis.

According to Christopherson[59], Bilharzia will not be eliminated as a national disease from Egypt by the application of antimony tartrate remedy, although supplemented by the hygienic measures suggested by Liper[61] for dealing with the all important mollusc; sound and thorough as they are.

It is true that the natives will co-operate in spite of religious prejudices, ignorance and primitive notions as shown by the fact that as many as 1000 cases of bilharzia appeared for treatment in both voluntary hospitals.[60]

In a series of 500 cases the treatment was as follows:

13	had	6	doses	amounting	to	12	grains	antimony	titrate
57	"	7	"	"	"	14.5	"	"	"
56	"	8	"	"	"	17	"	"	"
138	"	9	"	"	"	19.5	"	"	"
107	"	10	"	"	"	22	"	"	"
70	"	11	"	"	"	24.5	"	"	"
59	"	12+	"	"	"	27	"	"	"

348 (or 70%) of this number were pronounced cured.

In a total of 1000 cases there were 10 deaths attributed to the treatment or to the disease itself.

Many who applied for treatment were physical wrecks but not weeded out.

The method of administration is very simple. Tablets containing 10 grains each of antimony tartrate are dissolved in sterile solution so that 20 minims contain 1 grain, and this is injected into vein at elbow.

Complications resulting from bilharziosis, such as urinary fistulae and rectal papillomata, are greatly facilitated by the elimination of the causative factor. Before these injections, it required months to heal them after operation but now only about 20 days suffices.

Rectal cases showing friable, cauliflower tumors of the mucous membrane are treated by ligature and in case of small growths by removing as much as possible by scraping with the finger nail and swabbing with zinc chloride solution.

In the Katayama endemic district of Japan, according to Cort, it is now difficult to find the intermediate snail host infected with schistosomes.

A great reduction in morbidity and mortality followed control measures.

Conclusions

Medicines administered per ocem or subcutaneously for somatic and extra-intestinal helminthiasis have not been as sucessful as intestinal helminthiasis.

Cures of hookworms are frequently reported in large numbers but not justified in the name, if cure means freedom of the stools from ova.

There is no single drug or combination of drugs which act upon the parasite without disturbing the host.

Inconsistent results are obtained by various men in the field with the best known drugs, as for instance, thymol-chenopodium.

In the hands of many, chenopodium is preferred to thymol--useful in double infestations, has less systemic effects--less time required for individual treatment.

In the writer's experience, patients who had both thymol and oil of chenopodium, prefer the latter as it does not make them sick or keep them in bed.

Unofficially reported by Stiles, 72 deaths due to the oil of chenopodium.

Each field worker has his own theories regarding purgatives; no two men obtaining the same results. This also depends on local habits.

Recent work in bilharziosis marks a new era and appears to be a treatment par excellence for flukes. The method is simple and rapid, can inject hundreds of patients in a day. This will have a great medical and economic value as well as scientific interest.

The method of transmissions is known in all important helminth diseases. Each disease represents a different problem--but all along the same line--namely prevention. In such instances, where we do not have to deal with any specifically identical infections in any of the domesticated animals, the disease can be blotted out of existence.

The heavily infected cases of hookworm of the South have disappeared but Uncinariasis still exists and will exist because too much faith is being placed in drugs and too little knowledge of the sanitary conditions.

A great deal of valuable work is being published in journals which are not easily accessible to the physician.

The total evidence collected in this paper indicates that further work along this line is necessary and desirable.

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